Amendments to the Specification:

Please replace the text beginning on page 8, at [0063] and ending on page 13, at [0137] of the published Application with the following:

Example 1

4-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-en-1-ol, (VIa, X=X'=4-F; Y=Y'=R1=R2=R3=R4=H; m=n=1)

[0063] A solution containing 1-[bis-(4-fluorophenyl)methyl]piperazine (140 g, 0.485 mol), toluene (700 ml), (*Z*)-4-chloro-2-butene-1-ol (67.25 g, 0.631), and diisopropylethylamine (125.8 g, 0.971 mol) is stirred at 47-49°C. for 5 hrs. Water (350 ml) is added to the reaction mixture, the organic layer separated and the aqueous layer extracted with dichloromethane (2x200 ml). The combined organic layer is washed with water (200 ml), and concentrated to obtain crude product which is purified by flash column chromatography on silica gel using dichloromethane-methanol (9.6:0.4) as mobile phase to obtain pure product.

[0064] ^{1}H-NMR ($CDCl_3$, δppm): 2.15-2.80 (m, 8H), 3.01 (d, *J*=4.90 Hz, 2H), 4.13 (d, *J*=3.96 Hz, 2H), 4.20 (s, 1H), 5.55-5.75 (m, 1H), 5.75-6.00 (m, 1H), 6.96 (t, *J*=8.14 Hz, 4H), 7.20-7.40 (m, 4H).

Example 2

(*R,S*)-4-[4[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-en-1-ol, [VIb(R,S), X=Cl; X'=Y=Y'=R1=R2=R3=R4=H; m=n=1]

[0065] (*R,S*)-1-[(4-chlorophenyl)phenylmethyl]piperazine 8.0 g (mol) is converted to (*R,S*)-4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-en-1-ol in a manner similar to example 1. Crude product is obtained as a syrupy mass, which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase to obtain pure product.

[0066] ^{1}H-NMR ($CDCl_3$, δppm): 2.10-2.90 (m, 8H), 3.01 (d, *J*=5.75 Hz, 2H), 4.13 (d, *J*=-5.25 Hz, 2H), 4.19 (s, 1H), 5.50-5.75 (m, 1H), 5.75-6.00 (m, 1H), 7.00-7.40 (m, 9H).

Example 3

4-[4-Benzhydrylpiperazin-1-yl]-(*Z*)-but-2-en-1-ol, (VIc, X=X'=Y=Y'=H; R1=R2=R3=R4=H; m=n=1)

[0067] A solution containing 1-benzhydrylpiperazine (3 g, 0.0119 mol), toluene (20 ml), (*Z*)-4-chloro-2-butene-1-ol (1.65 g, 0.0155 mol), diisopropylethylamine (3.81 g, 0.0295 mol), and DMF (3 ml) is stirred at 55-60°C for 5 hrs. The reaction mass is quenched with water (20 ml), organic layer separated and the aqueous layer extracted with dichloromethane (2x20 ml). The organic extract is washed with water (10 ml), and concentrated to obtain crude product, which is purified by flash column chromatography on silica gel using dichloromethane-methanol (9.3:0.7) as mobile phase to obtain pure product.

[0068] ^{1}H-NMR ($CDCl_3$, δppm): 2.10-2.80 (m, 8H), 3.01 (d, J=5.52 Hz, 2H), 4.13 (dd, J_1=5.19 Hz, J_2=0.68 Hz, 2H), 4.21 (s, 1H), 5.50-5.75 (m, 1H), 5.75-6.00 (m, 1H), 7.00-7.50 (m, 10H).

Example 4

4-[4-[Bis(2,4-difluorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-en-1-ol, (VId, X=X'=Y=Y'=F; R1=R2=R3=R4=H; m=n=1)

[0069] 1-[Bis-(2,4-difluorophenyl)methyl]piperazine (20.0 g, 0.0617 mol) is converted to 4-[4-[bis(2,4-difluorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-en-1-ol in a manner similar to example 1. Crude product is obtained as a syrupy mass, which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase to obtain pure product.

[0070] ^{1}H-NMR ($CDCl_3$, δppm): 2.20-2.85 (m, 8H), 3.02 (dd, J_1=6.00 Hz, J_2=0.74 Hz, 2H), 4.14 (dd, J_1=5.31 Hz, J_2=0.98 Hz, 2H), 4.94 (s, 1H), 5.50-5.75 (m, 1H), 5.75-6.00 (m, 1H), 6.55-7.00 (m, 4H), 7.30-7.60 (m, 2H).

Example 5

4-[4-[Bis(4-chlorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-en-1-ol, (VIe, X=X'=Cl; Y=Y'=R1=R2=R3=R4=H; m=n=1)

[0071] 1-[Bis(4-chlorophenyl)methyl]piperazine (5.044 g, mol) is converted to 4-[4-[bis(4-chlorophenyl)methyl]piperazin-1-yl-(*Z*)-but-2-en-1-ol in a manner similar to example 1. The crude product obtained is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase to obtain pure product.

[0072] ^{1}H-NMR ($CDCl_3$, δppm): 2.10-2.80 (m, 8H), 3.01 (d, J=5.87 Hz, 2H), 4.13 (dd, J_1=5.26 Hz, J_2=0.88, 2H), 4.18 (s, 1H), 5.50-5.75 (m, 1H), 5.75-6.00 (m, 1H), 7.00-7.40 (m, 8H).

Example 6

[2-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-yl-methyl]phenyl]methanol (VIIIa, X=X'=F; Y=Y'=R1=R2=H; m=n=1, A=benzene ring)

[0073] 1-[Bis(4-chlorophenyl)methyl]piperazine (5.0 g, 0.0173 mol) is converted to [2-[4 [bis(4-fluorophenyl)methyl]piperazin-1-ylmethyl]phenyl]methanol using 2-(chloromethyl)benzyl alcohol, in a manner similar to example 1. The crude product obtained as brownish yellow syrup is purified by flash column chromatography on silica gel using toluene-methanol (9.2:0.8) as mobile phase to obtain pure product.

[0074] ^{1}H-NMR ($CDCl_3$, δppm): 2.00-2.80 (m, 8H), 3.6 (s, 2H), 4.18 (s, 1H), 4.57 (s, 2H), 6.70-7.03 (m, 4H), 7.05-7.40 (m, 8H).

Example 7

[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-ylmethyl]phenyl]methanol, (VIIIb, X=Cl; X'=Y=Y'=R1=R2=H; m=n=1, A=benzene ring)

[0075] 1-[Bis(4-chlorophenyl)methyl]piperazine (4.0 g, 0.0140 mol) is converted to [2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-ylmethyl]phenyl]methanol in a manner similar to example 1. The crude product obtained is purified by flash column chromatography on silica gel using toluene-methanol (9.2:0.8) as mobile phase to obtain pure product as a white foamy solid.

[0076] ^{1}H-NMR ($CDCl_3$, δppm): 2.00-2.80 (m, 8H), 3.60 (s, 2H), 4.16 (s, 1H), 4.56 (s, 2H), 6.86 (br, exchangeable by D_2O), 6.95-7.40 (m, 13H).

Example 8

4-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-yl]but-2-yn-1-ol (Xa, X=X'=4-F; Y=Y'=R—R2=H; m=1)

[0077] Method A: Using 4-chloro-2-butyne-1-ol

[0078] To a solution containing 1-[bis-(4-fluorophenyl)methyl]piperazine (300 g, 1.040 mol), tetrahydrofuran (1800 ml) and diisopropylethylamine (242.1 g, 1.873 mol) is added dropwise 4-chloro-2-butyne-1-ol (130.5 g, 1.248 mol) during 1 hr at 10-15°C. After stirring at 10-15°C for 1.5 hr the temperature is gradually raised to 25-30°C and stirred for further 7 hr. Thereafter, a solution of citric acid (437.3 g, 2.08 mol) in water (500 ml) is added and the mixture is concentrated under reduced pressure at below 60°C to remove most of the solvent. The resulting aqueous mass is washed with toluene (2x400 ml), basified to pH=9-10 and the product extracted into dichloromethane (2x.400 ml). The dichloromethane layer is washed with water (300 ml) and degassed to obtain crude product, which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase.

[0079] ^{1}H-NMR ($CDCl_3$, δppm): 1.84 (br, 1H, D_2O exchangeable), 2.20-2.80 (m, 8H), 3.31 (t, J=1.84 Hz, 2H), 4.21 (s, 1H), 4.29 (t, J=1.80 Hz, 2H), 6.80-7.05 (m, 4H), 7.10-7.50 (m, 4H).

[0080] Method B: Using 2-butyne-1,4-diol

[0081] A solution of methanesulfonyl chloride (48.69 g, 0.425 mol) and tetrahydrofuran (100 ml) is added dropwise to a stirred solution of 2-butyne-1,4-diol (10 g, 1.162 mol) and diisopropylethylamine (62.45 g, 0.483 mol) in tetrahydrofuran (400 ml) during 2 hr at 0-5°C. After 1 hr stirring at 0-5°C the temperature is raised to 25-30°C and stirred for further 1 hr. The reaction mixture is then cooled to 10-15°C, and to it is added diisopropylethylamine (99.34 g, 0.769 mol), followed by 1-[bis(4-fluorophenyl)methyl]piperazine (110.81 g, 0.384 mol) in portions during 30 min. The reaction mass is stirred at 10-15°C for 1 hr and then at 25-30°C for furthers 8 hrs. Toluene (500 ml) is added to it and the contents washed with water (2x400 ml). Thereafter, a solution of citric acid (161.52 g, 0.769 mol) in water (500 ml) is added and the mixture is concentrated under reduced pressure at below 60°C to remove most of the solvent. The resulting aqueous mass is washed with hexane (2x250 ml), basified to pH=9-10 and the product extracted into ethyl acetate (2x300 ml). The ethyl acetate layer is washed with water (200 ml) and degassed to obtain crude product which is purified by flash column chromatography on silica gel using toluene-methanol (9.3:0.7) as mobile phase to obtain pure product.

Example 9

(*R,S*)-4-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]but-2-yn-1-ol (by method A in Example 10), (Xb, X=Cl; X'=Y=Y'=R1=R2=H; m=1)

[0082] A solution containing (*R,S*)-1-[(4-chlorophenyl)phenylmethyl]piperazine (10 g, 0.0349 mol), toluene (50 ml), 4-chloro-2-butyne-1-ol (4.74 g, 0.0453 mol), and diisopropylethylamine (9.02 g, 0.0698 mol) is stirred at 45-50°C for 6 hrs. The reaction mixture is quenched with water (20 ml). The organic layer is separated and the aqueous layer extracted with dichloromethane (2x30 ml). The organic layers is washed with water (20 ml) and concentrated to obtain crude product as a syrupy mass, which is purified by flash column chromatography on silica gel using dichloromethane-methanol (9.6:0.4) as mobile phase to obtain pure product.

[0083] ^{1}H-NMR ($CDCl_3$, δppm): 1.88 (br, 1H), 2.20-2.75 (m, 8H), 3.31 (t, *J*=1.72 Hz, 2H), 4.20 (s, 1H), 4.29 (t, *J*=1.63 Hz, 2H), 7.05-7.50 (m, 9H).

Example 10

(*R,S*)-4-[4-[(4-fluorophenyl)phenylmethyl]piperazin-1-yl]but-2-yn-1-ol (by method B in Example 10), (Xc, X=F; X'=Y=Y'=R1=R2=H; m=1)

[0084] A solution of methanesulfonyl chloride (1.86 g, 16.27 mmol) and tetrahydrofuran (5 ml) is added dropwise to a stirred solution of 2-butyne-1,4-diol (3.82 g, 44.3 mmol) and diisopropylethylamine (6.30 g, 48.8 mmol) in tetrahydrofuran (20 ml) during 30 min at 0-5°C. After 1 hr stirring the temperature is raised to 25-30°C and stirred for further 1 hr. The resulting mixture containing mesylate of 2-butyne-1,4-diol is added dropwise to a stirred solution of (*R,S*)-1-[(4-fluorophenyl)phenylmethyl]piperazine (4.0 g, 14.79 mol) in tetrahydrofuran (25 ml) during 1 hr at 5-10°C. The reaction mass is stirred at 5-10°C for 1 hr and then at 25-30°C for further 5 hrs. Thereafter, citric acid (3.2 g, 0.01523 mol) is added and the mixture is concentrated under reduced pressure at below 60°C to remove most of the solvent. Water (50 ml) is charged to the residual mass and the resulting aqueous layer washed with hexane (2x30 ml), basified to pH=9-10 and the product extracted into dichloromethane (3x30 ml). The dichloromethane layer is washed with water (25 ml) and degassed to obtain crude product as a sticky solid, which is purified by flash column chromatography on silica gel using dichloromethane-methanol (9.2:0.8) as mobile phase to obtain pure product as a thick syrupy mass.

[0085] ^{1}H-NMR ($CDCl_3$, δppm): 1.87 (b), 2.25-2.70 (m, 8H), 3.30 (t, *J*=1.83 Hz, 2H), 4.2.1 (s, 1H), 4.29 (t, *J*=1.78 Hz, 2H), 6.85-7.02 (m, 2H), 7.13-7.42 (m, 7H).

Example 11

4-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-yl]-(*E*)-but-2-en-1-ol, (XIVa, X=X'=4-F; Y=Y'=R1=R2=R3=R4=H; m=n=1)

[0086] To a stirred solution of methyl 4-[4-[bis(4-fluorophenyl)methyl]piperazin-1-yl]-(*E*)-but-2-enoate (380 g, 0.984 mol) in tetrahydrofuran (1900 ml) at -10 to 0°C is added dropwise DIBALH (560 g, 3.938 mol, as 20% solution in toluene) during about 2-3 hrs. After completion of addition, the reaction mass is stirred for further 1.0 hrs at 0 to 10°C and then quenched by sequential addition of ethyl acetate (400 ml) and water (800 ml). After vigorous stirring for 2 hrs the mass is filtered. The organic layer is separated from the filtrate, washed with water (1500 ml) and concentrated to get crude product.

[0087] The crude product is taken in toluene (2000 ml), extracted into 10% acetic acid (2000 ml), the aqueous extract basified to pH 9-10 with 20% aqueous sodium hydroxide and the product extracted into dichloromethane (3x1500 ml). The dichloromethane layer is washed with water (800 ml), and concentrated to get a syrupy mass which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase.

[0088] ^{1}H-NMR ($CDCl_3$, δppm): 1.70 (br, D_2O exchangeable), 2.20-2.70 (m, 8H), 3.00 (d, *J*=5.38 Hz, 2H), 4.12 (d, *J*=4.40 Hz, 2H), 4.21 (s, 1H), 5.65-5.90 (m, 21), 6.85-7.05 (m, 4H), 7.28-7.40 (m, 4H).

Example 12

4-[4-[Bis-(4-fluorophenyl)methyl]piperazin-1-yl]-(*E*)-but-2-en-1-ol (XIa, X=X'=4-F; Y=Y'=R1=R2=H; m=1)

[0089] To a stirred solution of 4-[4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl]but-2-yn-1-ol (135 g, 0.379 mol) in tetrahydrofuran (4300 ml) at 5-10°C is added lithium aluminum hydride (43.1 g, 1.136 mol) in portions during 34 hrs. The reaction mixture is stirred for further 5-6 hrs. and then quenched by addition of ethyl acetate (135 ml), followed by water (100 ml) at 5-10°C. The resulting mixture is filtered, the organic layer separated from the filtrate, and concentrated to get crude product, which is purified by flash column chromatography on silica gel using toluene-

methanol (9:1) as mobile phase to obtain pure product.

[0090] ^{1}H-NMR ($CDCl_3$, δppm): 1.77 (br, D_2O exchangeable), 2.20-2.70 (m, 8H), 3.00 (d, *J*=4.91 Hz, 2H), 4.11 (d, *J*=3.71 Hz, 2H), 4.21 (s, 1H), 5.55-5.90 (m, 2H), 6.80-7.05 (m, 4H), 7.10-7.50 (m, 4H).

Example 13

(*R,S*)-4-[4[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*E*)-but-2-en-1-ol , (XIb, X=C1; X'=Y=Y'=R1=R2=H; m=1)

[0091] (*R,S*)-4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]but-2-yn-1-ol (3.5 g, mol) is converted to (*R,S*)-4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*E*)-but-2-en-1-ol in a manner similar to example 14. Crude product is obtained as a syrupy mass, which is purified by flash column chromatography on silica gel using toluene-methanol (9:1) as mobile phase to obtain pure product.

[0092] ^{1}H-NMR ($CDCl_3$, δppm): 2.20-2.65 (m, 8H), 3.00 (d, *J*=4.83 Hz, 2H), 4.11 (d, *J*=3.52 Hz, 2H), 4.20 (s, 1H), 5.60-5.90 (m, 2H), 7.00-7.50 (m, 9H).

Example 14

(*R,S*)-4-[4-[(4-fluorophenyl)phenylmethyl]piperazin-1-yl]-(*E*)-but-2-en-1-ol (XIc, X=F; X'=Y=Y'=R1=R2=H; m=1)

[0093] (*R,S*)-4-[4-[(4-fluorophenyl)phenylmethyl]piperazin-1-yl]but-2-yn-1-ol (2.13 g, 0.0063 mol) is converted to (*R,S*)-4-[4-[(4-fluorophenyl)phenyl-methyl]piperazin-1-yl]-(*E*)-but-2-en-1-ol in a manner similar to example 14. Crude product obtained is obtained as a syrupy mass which is purified by flash column chromatography on silica gel using dichloromethane-methanol (9.3:0.7) as mobile phase to obtain pure product.

[0094] ^{1}H-NMR ($CDCl_3$, δppm): 1.71 (br, exchangeable by D_2O), 2.10-2.70 (m, 8H), 3.00 (d, *J*=5.23 Hz, 2H), 4.11 (d, *J*=4.20 Hz, 211), 4.22 (s, 2H), 5.65-5.90 (m, 2M), 6.85-7.02 (m, 2H), 7.10-7.45 (m, 7H).

Example 15

Methyl 4-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-yl]-(E)-but-2-enoate, (XIIIa, X=X'=4-F; R=CH_3; Y=Y'=R1=R2=R3=R4=H; m=n=1)

[0095] A solution of methyl-4-bromocrotonate (46.56 g, 0.260 mol) in toluene (50 ml) is added dropwise to a mixture containing 1-[bis(4-fluorophenyl)methyl]piperazine (50 g, 0.173 mol), diisopropylethylamine (49.30 g, 0.381 mol) in toluene (250 ml) at 25-30°C during 30 minutes. After stirring for 8 hrs, the reaction mass is washed successively with water (2x150 ml), 0.2N hydrochloric acid (3x150 ml), and water (150 ml). To the organic layer at 5-10°C is added 3N hydrochloric acid (200 ml), stirred and the aqueous layer containing product is separated. It is then washed with toluene (200 ml), basified to pH=9-10 with 20% sodium hydroxide solution and the product extracted into ethyl acetate (2x150 ml). The organic layer is washed once with water (100 ml), concentrated and degassed. The residue is triturated with hexane (150 ml) and the solid filtered. The product is further purified by recrystallization from cyclohexane.

[0096] ^{1}H-NMR ($CDCl_3$, δppm): 1.63 (br, 1H, D_2O exchangeable), 2.20-2.65 (m, 8H), 3.13 (d, *J*=5.00 Hz, 2H), 3.72 (s, 3H), 4.22 (s, 1H), 5.88-6.03 (m, 1H), 6.80-7.05 (m, 5H), 7.20-7.40 (m, 4H).

Example 16

Methyl 4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*E*)-but-2-enoate- , (XIIIb, X=Cl; X'=Y=Y'=R1=R2=R3=R4=H; m=n=1)

[0097] A solution containing (*R,S*)-1-[(4-chlorophenyl)phenylmethyl]piperazine (5 g, 0.0174 mol), DMF (30 ml), methyl-4-bromocrotonate (4.7 g, 0.0263 mol), and diisopropylethylamine

(6.75 g, 0.0522 mol) is stirred at 27-30°C for 6 hrs. The reaction is quenched with water (40 ml) and the product extracted into dichloromethane (3x30 ml). The organic layer is washed with water (2x30 ml) and concentrated to obtain crude product which is purified by flash column chromatography on silica gel using ethyl acetate-hexane (6.5:3.5) as mobile phase to obtain pure product.

[0098] ^{1}H-NMR ($CDCl_3$, δppm): 2.20-2.65 (m, 8H), 3.14 (dd, J_1=6.20 Hz, J_2=1.39 Hz, 2H), 3.72 (s, 3H), 4.20 (s, 1H), 5.85-6.05 (m, 1H), 6.8-7.05 (m, 1H), 7.05-7.50 (m, 9H).

Example 17

[4-[4-[Bis(4-fluorophenyl)methyl]-piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid dihydrochloride, (Ia)

[0099] To a stirred solution of 4-[4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-en-1-ol (97.0 g, 0.271 mol) and potassium *tert*-butoxide (54.7 g, 0.487 mol) in anhydrous *tert*-butanol (776 ml), preheated at 60-65°C for 1 hr., under nitrogen atmosphere, is added dry sodium chloroacetate (63 g, 0.541 mol). The reaction mass is then refluxed for further 5 hrs. The mixture is then concentrated under reduced pressure at below 60°C until *tert*-butanol is completely removed. The residue is taken up in water (800 ml) and washed with ethyl acetate (2x500 ml). The aqueous solution is then acidified to pH 5-6, extracted into dichloromethane (3x500 ml), washed dichloromethane layer with water (300 ml), and concentrated to get crude product, whuch is purified by flash column chromatography on silica gel using toluene-methanol (4:1) as mobile phase to obtain pure product.

[0100] ^{1}H-NMR ($CDCl_3$, δppm): 2.40-2.80 (m, 4H), 2.80-3.20 (m, 4H), 3.65 (d, *J*=7.51 Hz, 2H), 3.96 (s, 2H), 4.19 (d, *J*=4.51 Hz, 2), 4.32 (s, 1H), 5.00-5.30 (m, 1H), 5.30-6.10 (m, 1H), 6.80-7.05 (m, 4H), 7.00-7.50 (m, 4H).

[0101] A suspension of [4-[4-[bis-(4-fluorophenyl)methyl]piperizin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid (83.8 g, 0.201 mol) and water (335 ml) is acidified under stirring to pH 1-2

with 6N hydrochloric acid at 25-30°C. The solution is filtered, concentrated under reduced pressure at below 50°C (until volume of solution is around 170 ml), and lyophilized to obtain the dihydrochloride salt.

Example 18

(*R,S*)-4-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid dihydrochloride, [Ib (R,S)]

[0102] (*R,S*)-4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-en-1-ol (100.0 g, 0.28 mol) is converted to (*R,S*)-[4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid in a manner similar to example 19. Crude product is obtained as a foamy solid which is purified by flash column chromatography on silica gel using toluene-methanol (4:1) as mobile phase to obtain pure product.

[0103] ^{1}H-NMR ($CDCl_3$, δppm): 2.40-2.75 (m, 4H), 2.75-3.20 (m, 4H), 3.62 (d, *J*=7.43 Hz, 2H), 3.95 (s, 2H), 4.17 (d, 3=4.9 Hz, 2H), 4.28 (s, 1H), 5.50-5.80 (m, 1H), 5.80-6.1 (m, 1H), 6.95-7.40 (m, 9H), 8.98 (br, exchangeable with D_2O)

[0104] It was converted to dihydrochloride salt as per example 17.

Example 19

[4-(4-Benzhydrylpiperazin-1-yl)-(*Z*)-but-2-enyloxy]acetic acid dihydrochloride, (Ic)

[0105] 4-(4-Benzhydrylpiperazin-1-yl)-(*Z*)-but-2-en-1-ol (2.1 g, 0.0065 mol) is converted to [4-(4-benzhydrylpiperazin-1-yl)-(Z)-but-2-enyloxy]acetic acid in a manner similar to example 17. The crude product obtained as a foamy solid is purified by flash column chromatography on silica gel using toluene-methanol (8.5:1.5) as mobile phase to obtain pure product.

[0106] ^{1}H-NMR ($CDCl_3$, δppm): 2.40-2.85 (m, 4H), 2.85-3.20 (m, 4H), 3.68 (d, *J*=7.53 Hz, 2H), 3.96 (s, 2H), 4.18 (d, *J*=4.60 Hz, 2H), 4.33 (s, 1H), 5.50-5.80 (m, 1H), 5.90-6.10 (m, 1H), 7.00-7.50 (m, 10H)

[0107] It is converted to dihydrochloride salt as per example 19.

Example 20

[4-[Bis(2,4-difluorophenyl)methyl]-piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid dihydrochloride, (Id)

[0108] 4-[4-[Bis(2,4-difluorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-en-1-ol (6.2 g, 0.0157 mol) is converted [4-[4-[bis(2,4-difluorophenyl)methyl]-piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid in a manner similar to example 17. Crude product is obtained is as a foamy solid which is purified by flash column chromatography on silica gel using toluene-methanol (4:1) as mobile phase to obtain pure product.

[0109] ^{1}H-NMR ($CDCl_3$, δppm): 2.20-2.75 (m, 4H), 2.75-3.20 (m, 4H), 3.57 (d, *J*=6.07 Hz, 2H), 3.96 (s, 2H), 4.17 (d, *J*=3.90 Hz, 2H), 4.99 (s, 1H), 5.50-6.10 (m, 2H), 6.45-7.0 (m, 4H), 7.20-7.65 (m, 2H), 9.87 (br)

[0110] The product is taken up in ethyl acetate (12 ml), acidified with a solution of anhydrous HCl in ethyl acetate to pH 1.0 to 2.0, concentrated and degassed to get the dihydrochloride salt.

Example 21

[4-[4-[Bis-(4-chlorophenyl)methyl]piperazin-1-yl]-(Z)-but-2-enyloxy]acetic acid dihydrochloride, (Ie)

[0111] 4-[4-[Bis(4-chlorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-en-1-ol (2.26 g, mol) is converted to [4-[4-[bis-(4-chlorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid in

a manner similar to example 17. Crude product obtained is purified by flash column chromatography on silica gel using toluene-methanol (4:1) as mobile phase to obtain pure product.

[0112] ^{1}H-NMR ($CDCl_3$, δppm): 2.50-2.80 (m, 4H), 2.80-3.20 (m, 4H), 3.60 (d, *J*=7.38 Hz, 2H), 3.94 (s, 2H), 4.20 (d, *J*=4.08 Hz, 2H), 4.31 (s, 1H), 5.23 (br, exchangeable with D_2O), 5.50-5.80 (m, 1H), 5.80-6.10 (m, 1H), 7.10-7.40 (m, 8H).

[0113] The product was converted to dihydrochloride salt as in example 17.

Example 22

[4-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-yl}-(*Z*)-but-2-enyloxy]acetic acid methyl ester dihydrochloride, (If)

[0114] To a stirred solution of [4-[4-[bis(4-fluorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid (35 g, 0.084 mol) in methanol (560 ml), is added a solution of anhydrous HCl in ethyl acetate till pH is 1-2. The solution is refluxed for 2 hrs, cooled to 25-30°C and stirred for 4 hrs. The crystallized solid is filtered, washed with ethyl acetate (2x5 ml), and dried in oven at 60-65°C to get the product.

[0115] ^{1}H-NMR (D_2O, δppm): 3.20-3.60 (m, 8H), 3.64 (s, 3H), 3.94 (d, *J*=7.66 Hz, 2H), 4.00-4.20 (m, 4H), 5.31 (s, 1H), 5.50-5.78 (m, 1H), 5.90-6.20 (m, 1H), 6.85-7.15 (m, 4H), 7.30-7.60 (m, 4H).

Example 23

[4-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid ethyl ester dihydrochloride, (Ig)

[0116] To a stirred solution of [4-[4-[bis(4-fluorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid (1.0 g, 0.0024 mol) in ethanol (20 ml), is added a solution of anhydrous ethanolic HCl till pH is 1-2. The solution is refluxed for around 2 hrs, cooled to 25-30°C and stirred for 4 hrs. The crystallized solid is filtered, washed with ethanol (2x5 ml), and dried in oven at 60-65°C to get the product.

[0117] ^{1}H-NMR ($CDCl_3$+DMSO-d_6, δppm): 1.28 (t, *J*=7.10 Hz, 3H), 2.70-4.30 (m, 17H), 5.70-6.20 (m, 2H), 7.10 (t, *J*=8.62 Hz, 411), 7.40-7.80 (m, 4H).

Example 24

[4-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid isopropyl ester dihydrochloride, (Ih)

[0118] To a stirred solution of [4-[4-[bis(4-fluorophenyl)methyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid (1.0 g, 0.0024 mol) in isopropyl alcohol (20 ml), is added a solution of anhydrous HCl in isopropyl alcohol till pH of solution is 1-2. The solution is refluxed for around 2 hrs, cooled to 25-30°C and stirred for 4 hrs. The crystallized solid is filtered, washed with isopropyl alcohol (2x5 ml), and dried in oven at 60-65°C to get product 0.968 g (75.85% yield).

[0119] ^{1}H-NMR ($CDCl_3$+DMSO-d_6, δppm): 1.23 (d, *J*=6.25 Hz, 6H), 2.60-3.70 (m, 8H), 3.70-4.40 (m, 7H), 4.80-5.20 (m, 1H), 5.60-5.90 (m, 1H), 5.90-6.10 (m, 1H), 7.16 (t, *J*=8.56 Hz, 4H), 7.40-7.90 (m, 4H).

Example 25

(*R,S*)-[4[-4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid isopropyl ester dihydrochloride, (Ii)

[0120] The preparation was carried out using (*R,S*)-[4-[4-[(4-chlorophenyl)-phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid in a manner similar to example 24.

[0121] ^{1}H-NMR ($CDCl_3$+DMSO-d_6, δppm): 1.26 (d, *J*=6.26 Hz, 6H), 2.80-3.70 (m, 8H), 3.80-4.15 (m, 3H), 4.21 (d, *J*=5.57 Hz, 4H), 4.90-5.15 (m, 1H), 5.70-5.95 (m, 1H), 5.95-6.15 (m, 1H), 7.10-7.90 (m, 9H).

Example 26

(*R,S*)-[4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid methyl ester dihydrochloride, (Ij)

[0122] To a stirred solution of (*R,S*)-[4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid (1 g, 0.0024 mol) in methanol (20 ml), is added a solution of anhydrous HCl in ethyl acetate till pH of the solution is 1-2. The solution is refluxed for 2 hrs, cooled to 25-30°C, added anhydrous diethyl ether till slight haziness and stirred for 4 hrs. The crystallized solid is filtered, washed with diethyl ether (2x5 ml), and dried in oven at 60-65°C to get product.

[0123] ^{1}H-NMR ($CDCl_3$+DMSO-d_6, δppm): 3.10-3.90 (m, 8H), 3.73 (s, 3H), 3.90-4.30 (m, 7H), 5.70-6.00 (m, 1H), 6.00-6.20 (m, 1H), 7.10-7.50 (m, 5H), 7.50-8.00 (m, 4H).

Example 27

(*R,S*)-[4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid ethyl ester dihydrochloride, (Ik)

[0124] The preparation was carried out using (*R,S*)-[4-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]-(*Z*)-but-2-enyloxy]acetic acid in a manner similar to example 25, to obtain the product.

[0125] ^{1}H-NMR ($CDCl_3$+DMSO-d_6, δppm): 1.27 (t, *J*=7.12 Hz, 3H), 3.10-3.90 (m, 8H), 3.90-4.30 (m, 9H), 5.75-5.95 (m, 1H), 5.95-6.15 (m, 1H), 7.10-7.50 (m, 5H), 7.50-8.00 (m, 4H).

Example 28

[2-[4-[bis(4-fluorophenyl)methyl]piperazin-1-ylmethyl]benzyloxy]acetic acid dihydrochloride, (IIa)

[0126] [2-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-ylmethyl]phenyl]methanol (5.0 g, 0.0122 mol) is converted to [2-[4-[Bis(4-fluorophenyl)methyl]piperazin-1-ylmethyl]benzyloxy]acetic acid in a manner similar to example 17. Crude product obtained is purified by flash column chromatography on silica gel using toluene-methanol (8.5:1.5) as mobile phase to obtain pure product as a white foamy solid.

[0127] $_{1}$H-NMR ($CDCl_3$, δppm): 2.40-2.75 (m, 4H), 2.75-3.20 (m, 4H), 4.06 (s, 2), 4.10 (s, 2H), 4.28 (s, 1H), 4.58 (s, 2H), 6.70-7.10 (m, 4H), 7.10-7.50 (m, 8H).

[0128] The product is taken up in ethyl acetate (12 ml), acidified with a solution of anhydrous HCl in ethyl acetate to pH 1.0 to 2.0, concentrated and degassed to get dihydrochloride salt as a white solid.

Example 29

(*R,S*)-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-ylmethyl]benzyloxy]acetic acid dihydrochloride, (IIb)

[0129] [2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-ylmethyl]phenyl]methanol (4.0 g, 9.83 mmol) is converted to [2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-ylmethyl]benzyloxy}acetic acid in a manner similar to example 17. Crude product obtained as an off-white foamy solid is purified by flash column chromatography on silica gel using toluene-methanol (8.5:1.5) as mobile phase to obtain pure product as a white foamy solid.

[0130] ^{1}H-NMR ($CDCl_3$, δppm): 2.40-2.80 (m, 4H), 2.80-3.20 (m, 4H), 4.06 (s, 2H), 4.14 (s, 2H), 4.28 (s, 1H), 4.58 (s, 2H), 7.00-7.50 (m, 13H).

[0131] The product is converted to dihydrochloride salt using a solution of anhydrous HCl in ethyl acetate as in example 28.

Example 30

[4-[4-[Bis(4-fluorophenyl)methyl]piperizin-1-yl]-(*E*)-but-2-enyloxy]acetic acid dihydrochloride, (IIIa)

[0132] To a stirred solution of 4-[4-[bis(4-fluorophenyl)methyl]piperazin-1-yl]-(*E*)-but-2-en-1-ol (247.0 g, 0.689 mol) and potassium *tert*-butoxide (139.2 g, 1.240 mol) in anhydrous *tert*-butanol (2000 ml), preheated at 60-65°C for 1 hr. under nitrogen atmosphere, is added dry sodium chloroacetate (160.5 g, 1.378 mol). The reaction mass is then refluxed for further 5 hrs. The mixture is then concentrated under reduced pressure at below 60°C until *tert*-butanol is completely removed. The residue is taken up in water (1500 ml) and washed with ethyl acetate (2x1500 ml). The aqueous solution is then acidified to pH 5-6, extracted into dichloromethane (2x750 ml), washed dichloromethane layer with water (300 ml), and concentrated to get crude product as a foamy solid. The crude product is purified by flash column chromatography on silica gel using toluene-methanol (4:1) as mobile phase. The product was converted to its dihydrochloride salt as in example 17.

[0133] ^{1}H-NMR (D_2O, δppm): 3.20-3.70 (m, 8H), 3.82 (d, *J*=6.79 Hz, 2H), 3.93-4.05 (m, 4H), 5.35 (s, 1H), 5.65-5.80 (m, 1H), 5.97-6.12 (m, 1H), 6.80-7.00 (m, 4H), 7.36-7.50 (m, 4H).

Example 31

(*R,S*)-[4-[4-[(4-Chlorophenyl)phenylmethyl]piperizin-1-yl]-(*E*)-but-2-enyloxy]acetic acid dihydrochloride, (IIIb)

[0134] (*R,S*)-4-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]-(*E*)-but-2-en-1-ol (1.9 g, 0.0053 mol) is converted to (*R,S*)-[4-[4-[(4-Chlorophenyl)phenylmethyl]piperizin-1-yl]-(*E*)-but-2-enyloxy]acetic acid as in example 30. Crude product is obtained as a foamy solid which is purified by flash column chromatography on silica gel using toluene-methanol (8:2) as mobile phase to obtain pure product.

[0135] ^{1}H-NMR ($CDCl_3$, δppm): 2.40-2.75 (m, 4H), 2.75-3.20 (m, 4H), 3.30-3.50 (m, 2H), 3.93 (s, 2H), 4.00-4.15 (m, 2H), 4.26 (s, 1H), 5.70-6.00 (m, 21), 6.82 (br), 7.00-7.50 (m, 9H)

[0136] It was converted to dihydrochloride salt as per example 17.

Example 32

(*R,S*)-[4-[4-[(4-fluorophenyl)phenylmethyl]piperazin-1-yl]-(*E*)-but-2-enyloxy]acetic acid dihydrochloride, (IIIc)

[0137] (*R,S*)-4-[4-[(4-Fluorophenyl)phenylmethyl]piperazin-1-yl}-(*E*)-but-2-en-1-ol (0.7 g, 2.06 mmol) is converted to (*R,S*)-[4-[4-[(4-fluorophenyl)phenylmethyl]piperizin-1-yl]-(*E*)-but-2-enyloxy]acetic acid as per example 30. The crude product obtained (0.77 g) is purified by flash column chromatography on silica gel using toluene-methanol (3:2) as mobile phase to obtain pure product.

[0138] ^{1}H-NMR ($CDCl_3$, δppm): 2.40-3.20 (m, 8H), 3.20-3.50 (m, 2H), 3.92 (s, 2H), 4.00-4.15 (m, 2H), 4.26 (s, 1H), 5.65-5.95 (m, 2H), 6.80-7.03 (m, 2H), 7.07-7.50 (m, 7H), 10.70 (br, exchangeable).